REMARKS

The status of the application is as follows:

- Original Claims 1-12 were presented for prosecution.
- Original Claims 7 and 12 were withdrawn from consideration by the Examiner as being drawn to non-elected subject matter, and were cancelled by the Applicant
- Original Claims 1-6 and 8-11 were previously amended and are further amended herein.
- Original Claims 1-6 and 8-11 were rejected by the Examiner.
- Original Claims 1-6 and 8-11 presently remain pending for reconsideration by the Examiner.

The Examiner rejected Claims 1-6 and 8-11 under 35 U.S.C. 101, because the specification did not provide an asserted or a well-established utility for the invention *as claimed*.

The Examiner rejected Claims 1-6 and 8-11 under 35 U.S.C. 112, first paragraph, for lack of enablement, because, in the absence of an asserted or well-established utility for the invention *as claimed*, one skilled in the art would not know how to use the claimed invention.

The Examiner rejected Claims 1-6 and 8-11 under 35 U.S.C. 112, second paragraph, for lack of clarity of certain terms.

Applicant respectfully replies to the Examiner's 35 U.S.C. 101 and 35 U.S.C. 112, first and second paragraph rejections, and requests continued examination and reconsideration in light of the foregoing amendments and accompanying remarks that follow. In view of the amendments herein, applicant respectfully submits that all of the pending claims are allowable over the prior art of record.

REMARKS REGARDING TELEPHONIC CONFERENCE WITH THE EXAMINER

Applicants' attorney wishes to thank the Examiner for his courtesy and time during a telephone interview that was held on February 23, 2007. The Examiner's comments and insight were very helpful in preparing this response. It is intended that the comments below reflect the substance and spirit of that interview.

Pursuant to the comments and insights of the Examiner, applicants' attorney concurred with the Examiner that the term "mutually exclusive domain molecular switch" was descriptive of the *function* of the invention, which invention, the Examiner properly characterized as a fusion protein.

Pursuant to the comments and insights of the Examiner, applicants' attorney distinguished the terms

- "surface loop",
- "surface loop amino acid",
- "first/second surface loop amino acid"

from one another and agreed to amend the specification to more clearly assert the distinctions among these terms.

Pursuant to the comments and insights of the Examiner, applicants' attorney clarified the meaning of the term "folding domain molecular switch" for the Examiner.

Pursuant to the comments and insights of the Examiner, applicants' attorney distinguished the terms

- "domain,"
- "folding domain,"
- "insert domain,"

- "target domain,"
- "regulatory domain,"
- "cytotoxic or catalytic domain,"

from one another and agreed to amend the specification to more clearly assert the distinctions among these terms.

Pursuant to the comments and insights of the Examiner, applicants' attorney agreed to define and use the terms

- "ubiquitin insert protein,"
- "insert regulatory domain,"
- "barnase target protein,"
- "target cytotoxic domain"

and agreed to amend the specification to more clearly assert the distinctions among these terms.

Pursuant to the comments and insights of the Examiner, applicants' attorney clarified the location of the "ubiquitin regulatory domain" as lying anywhere between the amino terminus and carboxyl terminus of the "ubiquitin insert protein."

Pursuant to the comments and insights of the Examiner, applicants' attorney clarified the location of the insertion point of the ubiquitin insert protein within the surface loop of the barnase target protein.

REMARKS REGARDING AMENDMENT OF THE TITLE

The amendment to the title of the invention claimed herein more accurately describes the subject matter of the invention herein. The amendment to the title should not be construed as disclaiming any patentable subject matter disclosed in the specification.

REMARKS REGARDING AMENDMENT OF THE ABSTRACT OF THE DISCLOSURE

The amendment to the abstract of the disclosure more accurately describes the subject matter of the invention herein. The amendment to the abstract of the disclosure should not be construed as disclaiming any patentable subject matter disclosed in the specification.

REMARKS REGARDING AMENDMENT OF THE SPECIFICATION

The amendments to the specification more accurately describe the subject matter of the invention herein. The amendments to the specification should not be construed as disclaiming any patentable subject matter disclosed in the specification.

REMARKS RESPONSIVE TO EXAMINER'S OBJECTION

The Examiner objected to the disclosure because the detailed description did not include a description for element #25 as shown in Fig. 1B; therefore it could not be determined what element #25 is intended to represent [DETAILED ACTION: Page 2; Last Full Paragraph]

In response, Applicants have amended the specification herein to advise that:

"In Fig. 1B, reference numeral 25 refers to the amino-carboxyl length of insert regulatory domain of insert protein barnase in its folded conformation (corresponding to double-headed arrow labeled 38 Å in FIG. 2A). [APPENDIX A herein at *clean* ¶ [00040] and APPENDIX B herein at correspondingly *marked* ¶ [00040]]

REMARKS RESPONSIVE TO 35 U.S.C. § 101 REJECTION

The Examiner rejected Claims 1-6, 8-ii under 35 U.S.C. 101, because the specification did not provide either an asserted or a well-established utility for the invention as claimed. [DETAILED ACTION: PAGE 3]

In response, the applicant has, without adding any new matter, amended the claims so that the ubiquitin-barnase fusion protein claimed herein is supported by the following specific, substantial and credible utility, derived from the juxtaposition of paragraph [0004] of the instant application as published and paragraph [0070] of the instant application ***as published***:

> "**[0004]** Ribonucleases are hydrolase enzymes that break linkages between nucleotides in ribonucleic acid. They are accordingly highly cytotoxic. A major problem with their use as therapeutic agents, for example, as pharmacologic agents in the treatment of cancer, is that their cytotoxicity is indiscriminate. Currently available ribonuclease pharmacologic agents kill normal as well as neoplastic cells, and the side effects of their use can be severe. Additionally, currently available ribonuclease agents demonstrate poor bioavailability owing to their rapid degradation by the liver and their difficulty in passing through both normal and neoplastic cell membranes.
>
> **[0070]** Consequently, the regulatory domain of ubiquitin and the catalytic domain of barnase cannot simultaneously co-exist in their folded states; and, **the regulatory domain of ubiquitin, may be used to regulate the cytotoxic activity of barnase**. Moreover, the ubiquitin and barnase domains participate in a cooperative and reversible conformational equilibrium that may be influenced and controlled by a variety of controllable effector signals such as, for example, ligand binding, pH, temperature, chemical denaturants, or the presence of stabilizing or destabilizing mutations in either the barnase or ubiquitin domains. [Emphasis provided]"

REMARKS RESPONSIVE TO 35 U.S.C. § 112 FIRST PARAGRAPH REJECTION

The Examiner rejected Claims 1-6, 8-11 under 35 U.S.C. 112, first paragraph for lack of enablement, because, in the absence of either an asserted or well-established utility for the invention as claimed, one skilled in the art would not know how to use the claimed invention. [DETAILED ACTION: PAGE 3]

In response, the applicant has, without adding any new matter, amended the claims so that the ubiquitin-barnase fusion protein claimed herein is supported by the specific, substantial and credible utility, recited in the foregoing section. Applicants respectfully submit that satisfaction of the utility requirement herein will operate to satisfy the dependent enablement requirement herein.

REMARKS RESPONSIVE TO 35 U.S.C. § 112 SECOND PARAGRAPH REJECTIONS

The Examiner rejected Claims 1-6, 8-11 under 35 U.S.C. 112 Second Paragraph because the application did not appear to clarify conflicting claim language as it pertained to the terms "surface loop," and "surface loop amino acid," further asserting that it was unclear whether the "first surface loop" and "first surface loop amino acid" are in fact the same thing or distinct elements of the invention. [DETAILED ACTION: PAGE 4]

Having earlier defined a "surface loop as follows:

> "The tertiary structure of a protein may contain a surface loop. As used herein, the term surface loop means a continuous length of polypeptide chain whose constituent amino acids are in neither an alpha helical conformation nor in a beta sheet conformation, and can contact at least five water molecules, as determined by the DSSP computer program of Wolfgang Kabsch and Chris Sander. The DSSP, a program which is well known in the art, defines secondary structure, geometrical features and solvent exposure of proteins, given atomic coordinates in Protein Data Bank format, which is also well known in the art. (W. Kabsch & C. Sander, "Dictionary of protein secondary structure: pattern recognition of hydrogen-bonded and geometrical figures", Biopolymers 22, 2577-2637. (1983); See also, Centre for Molecular and Biomolecular Informatics, University

of Nijmegen, Toernooiveld 1, P.O. Box 9010, 6500 GL Nijmegen, +31 (0)24-3653391." [Paragraph [0034] of Application *as Published*]

The following clarification has been added to the specification herein:

"Consistently with the foregoing definition, the term "surface loop" additionally means the target cytotoxic domain of the barnase target protein, beginning at an alpha carbon of an initial amino acid of the surface loop and terminating at an alpha carbon of a terminal amino acid of the surface loop." [APPENDIX A herein at *clean* ¶ [00025] and APPENDIX B herein at correspondingly *marked* ¶ [00025]]

Moreover, in the amended specification:

- The term "**first** surface loop amino acid" has been stricken and been replaced by the term "alpha carbon of an **initial** amino acid of the surface loop; and,
- The term "**second** surface loop amino acid" has been stricken and been replaced by the term "alpha carbon of a **terminal** amino acid of the surface loop,

to more clearly distinguish the amino acid at which the surface loop (of amino acids) begins from amino acid at which the surface loop (of amino acid) ends. [Emphasis provided]

The Examiner also rejected Claims 1-6, 8-11 under 35 U.S.C. 112 Second Paragraph because of an apparent confusion regarding the intended meaning of the term "folding domain molecular switch" and whether the mutual exclusivity of the molecular arises between "regulatory domains, folding domains, fusion proteins, target proteins, etc." [DETAILED ACTION: PAGE 5; First Full Paragraph]

In response, applicants have amended the specification and claims herein to clarify that the mutual exclusivity arises between an:

- "insert regulatory domain" of a "ubiquitin insert protein"

that is inserted within a "surface loop" comprising a

- "target cytotoxic domain" of a "barnase target protein,"

which proteins comprise the ubiquitin-barnase fusion protein of the invention [APPENDIX A hereto at *clean* ¶ [00033] and APPENDIX B hereto at correspondingly *marked* ¶ [00033]]

The Examiner further rejected Claims 1-6, 8-11 under 35 U.S.C. 112 Second Paragraph because it was "unclear whether the regulatory domain [of the ubiquitin insert protein] lies anywhere between the amino terminus and the carboxy[l] terminus, in a specific location, or otherwise." [DETAILED ACTION: PAGE 5; First Full Paragraph]

In response, during their telephone conference, applicants' attorney referred the Examiner to paragraph [00041] of the application as published, wherein it was stated that:

> [00041] [i] an exemplary insert protein having an insert domain lying between an amino terminal and a carboxyl terminal, which insert domain is associated with a first quantity of free energy … "
>
> to establish that the regulatory domain [of the ubiquitin insert protein] lies **anywhere** between the amino terminus and the carboxyl terminus of the ubiquitin insert protein.

Applicants have additionally amended the foregoing quoted sentence fragment as follows:

> "(a) ubiquitin insert protein having an insert regulatory domain lying anywhere between an amino terminal and a carboxyl terminal of the ubiquitin insert protein, which insert regulatory domain is associated with a first quantity of free energy … "
> [APPENDIX A herein at *clean* ¶ [0031] and APPENDIX B herein at correspondingly *marked* ¶ [0031]]

to make clear that the insert regulatory domain of the ubiquitin insert protein] lies **anywhere** between the amino terminus and the carboxyl terminus of the ubiquitin insert protein.